Remarks

Claims 1-3, 5-11, 18, 19, 21-36 and 51-58 are pending in the present application. Claims 18 and 19 are withdrawn, and claims 1-3, 5-11, 21-36 and 51-58 are examined in the present application.

Applicants acknowledge with appreciation the indication of the withdrawal of the rejections under 35 U.S.C. § 112, 2nd paragraph, the rejections under 35 U.S.C. § 102, and certain of the rejections under 35 U.S.C. § 103(a). The remaining/new rejections under 35 U.S.C. § 103(a) are addressed below.

Rejections under 35 U.S.C. § 103(a)

A. Bettinotti et al. in view of Sapolsky et al. and Guo et al.

Claims 1-3, 5-11, 21-36, 51 and 55 are rejected under 35 U.S.C. § 103(a) over Bettinotti et al. (1997) in view of Sapolsky et al. (1997, EP 0 785 280 A2) and Guo et al. (1994).

Applicants respectfully maintain that the skilled artisan would not be motivated to combine nor have a reasonable expectation of success in combining the teachings of Bettinotti et al. with Sapolsky et al. to form the microarray taught by Applicants. Specifically, Bettinotti et al. only discusses direct sequencing of HLA loci, and Sapolsky et al. only discusses detection of single-base polymorphisms in a stretch of nucleotides, which Applicants maintain is not applicable to the highly polymorphic HLA loci, as discussed below.

Sapolsky et al. explains in the paragraph on page 2, lines 27-36: "In the human genome, *single-base polymorphisms occur roughly once per 300 bp*," and "*useful* polymorphisms...can be found approximately *once per kilobase*." (emphasis added). The design of the arrays in Sapolsky et al. follows this underlying theory, and the probes are designed to detect a single nucleotide polymorphism among a stretch of sequence (see, for example, Figure 3).

The examiner maintains a broad interpretation of Sapolsky et al., i.e., that the detection of single-base polymorphisms found in Sapolsky et al. are broadly applicable to "the detection of any particular nucleotide sequence by probe hybridization" (Office Action on Page 10, emphasis added), and, on this basis, concludes that one of skill in the art would be motivated to use the methods of Sapolsky et al. to design microarray probes corresponding to the highly polymorphic HLA loci. Applicants respectfully disagree.

In contrast to the single nucleotide polymorphisms screened in the methods of Sapolsky et al., and as noted in Applicants' specification on page 2, lines 14-15, "The human major histocompatibility genes are among the most polymorphic genes known in the human genome." Applicants' arrays for typing HLA loci have to account for this high level of polymorphism in their probe designs, and how Applicants have succeeded in overcoming this challenge is disclosed in the specification as filed: "The key feature of the oligonucleotide array assay is the high redundancy of oligonucleotide probes." (page 33, lines 14-15).

With respect to the Bettinotti et al. reference, instead of describing probes to identify specific alleles, Bettinotti et al. uses nested pcr with primers spanning regions of the HLA loci, and directly sequences the pcr products. Even with this approach, Bettinotti notes: "The real challenge was to find a combination of primers that could effectively amplify all alleles at a given locus." (page 427, right column, middle of second paragraph) (emphasis added). Thus, consistent with this statement from Bettinotti, the skilled artisan would not have had a reasonable expectation of success of using the arrays detailed in Sapolsky et al. to analyze the highly polymorphic HLA loci.

Therefore, Applicants respectfully maintain that, even without the recited the density limitations, claims 1-3, 5-11, 21-36, 51 and 55 are not obvious over Bettinotti et al. in view of Sapolsky et al., and the elements/suggestions missing from these references are not provided by Guo et al.

The Guo et al. reference discusses the optimization of the surface density of an array of 15mer oligonucleotides with 15mer oligo dT spacers, representing 5 point mutations from exon 4 of the human tyrosinase gene (see Table 1, page 5459). On page 5460, Guo et al. concludes that an optimum surface density for this system is approximately 500 angstrom^2/molecule, occurring at about 5mM oligonucleotide concentration (see also Figure 3b, page 5461). Further testing reported in Guo et al. used this optimal concentration of 5mM oligonucleotide. Guo et al. notes on page 5459, second column, that the "surface density of the oligonucleotide probe" is "an important parameter," evidencing the criticality of the claimed density range.

Importantly, the spots used by the Guo et al. reference were 3 millimeters wide (see page 5458, bottom of left column). There is no teaching or suggestion found in this combination of references that a density used for hybridization to 3 millimeter spots would be reasonably

expected to be successful in creating a *micro*array.

In light of the above discussion, Applicants respectfully assert that the combination of Bettinotti et al., Sapolsky et al. and Guo et al. is insufficient to present a *prima facie* showing of obviousness. Therefore, it is respectfully requested that this rejection of claims 1-3, 5-11, 21-36, 51 and 55 under § 103(a) be withdrawn.

B. Bettinotti et al. in view of Sapolsky et al., Guo et al. and Brown et al.

Claims 52-54 and 56-58 are rejected under 35 U.S.C. § 103(a) over Bettinotti et al. (1997) in view of Sapolsky et al. (1997, EP 0 785 280 A2) and Guo et al. (1994), and further in view of Brown et al. (1998, U.S. Patent No. 5,807,522).

For the reasons stated above with respect to claims 1-3, 5-11, 21-36 51 and 55, claims 52-54 and 56-58 are not obvious over the combination of Bettinotti et al., Sapolsky et al. and Guo et al., and the elements and suggestions missing from these references are not provided by Brown et al.

In addition, claims 52-54 and 56-58 contain the limitations that the oligonucleotides are covalently attached to the solid support with a linking group comprising an aminoalkylsilane and a phenylenediisothiocyanate. Applicants find no reason to motivate one of skill in the art to modify the microarray of Brown et al. with the microarray chemistry of aminoalkylsilane, particularly when the arrays of Brown et al. were accomplished by the simple method of coating a glass surface with poly-l-lysine (see column 7, lines 40-45; column 16, lines 22-39).

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR International Co. v. Teleflex Inc., et al., Slip Op. at 15, 550 U.S. ___, 127 S.Ct. 1727 (April 30, 2007) (emphasis added).

In addition, Applicants' disclosure did not use the identical methods found in the Guo et al. reference to create the disclosed *micro*arrays (note that Dr. Guo is also a listed inventor of the present application).

Guo et al. discusses an array of oligonucleotides prepared by immersing pre-cleaned microscope slides in 1% 3-aminopropyltrimethoxysilane solution for 2 minutes. In contrast, Applicants' specification teaches of a vapor deposition of the aminoalkyltrialkoxysilane. As discussed on page 27 of the Applicants' specification, the use of a vapor phase deposition of the aminoalkyltrialkoxysilane surprisingly resulted in a particularly uniform surface for probe assembly and presentation, *allowing for a more dense array of oligonucleotide probes* than the methods discussed in the Guo et al. reference.

In light of the above discussion, Applicants respectfully assert that the combination of Bettinotti et al., Sapolsky et al., Guo et al. and Brown et al. is insufficient to present a *prima facie* showing of obviousness with respect to claims 52-54 and 56-58. Therefore, it is respectfully requested that this rejection of claims 52-54 and 56-58 under § 103(a) be withdrawn.

Conclusion

In light of the foregoing, an early and favorable reconsideration and allowance of the pending claims is respectfully requested.

Respectfully submitted,

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